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ORIGINAL ARTICLE

Value of conventional and tissue Doppler echocardiography in the estimation of left ventricular filling pressure

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KEYWORDS
Left ventricular filling pressure;
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Abstract *Background:* Various conventional and tissue Doppler parameters have been proposed for the estimation of left ventricular filling pressure.
Aim: To assess the utility of several conventional and tissue Doppler parameters in the estimation of left ventricular end diastolic pressure (LVEDP).
Method: Among 40 consecutive patients LVEDP was correlated with pulsed Doppler of mitral inflow and pulsed tissue Doppler of lateral mitral annulus.
Results: Among all studied Doppler variables, E'/A' ratio showed the most significant correlation with LVEDP ($r = 0.612$, $p < 0.001$). Among patients with grade II and III diastolic dysfunction, E'/A' ratio showed the best correlation with LVEDP ($r = 0.81$, $p < 0.001$) with the following regression equation: LVEDP = 1.77 + (20.4 × E'/A') while in patients with grade I diastolic dysfunction no correlation exists ($r = 0.11$, $p = 0.63$). Weak significant correlation was detected between E/E' ratio and LVEDP ($r = 0.382$, $p = 0.016$). An E/E' ratio > 12 had 25% sensitivity and 100% specificity to identify patients with elevated LVEDP (> 15 mm Hg) with a positive predictive value of 100%. On the other hand, an E/E' ratio of < 8 had 77% sensitivity and 57% specificity to identify patients with normal LVEDP with a negative predictive value of 31%.

Abbreviations: DT, deceleration time; IR, impaired relaxation; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; LVEDP, left ventricular end diastolic pressure; PCWP, pulmonary capillary wedge pressure; TDI, tissue Doppler imaging.

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Conclusion: Of all echocardiographic variables investigated, E'/A' ratio was identified as the best index to estimate LVEDP especially in patients with advanced LV diastolic dysfunction; a relation that was not found for other conventional or tissue Doppler variables including the E/E' ratio.

1. Background

Estimation of left ventricular (LV) filling pressure is important not only for the diagnosis but also to predict prognosis of different cardiac diseases and to guide therapeutic strategy.[1,2] Invasive measurement is the gold standard for determining LV filling pressure; however invasive assessment is not practical given the potential complications, cost, and the difficulty to be undertaken as a continuous measure to guide therapy. Although various noninvasive methods have been proposed to translate conventional Doppler assessments of transmitral and pulmonary venous flow into measures of LV filling pressure, these methods have not been accurate when applied to a wide range of patients.[3,4]

Tissue Doppler imaging (TDI) of mitral annular motion has been proposed as a better echocardiographic modality to estimate LV filling pressure. The relationship between blood flow derived velocities and regional myocardial wall motion derived velocities, expressed as the E/E' ratio, has been shown in a number of studies to be useful in estimating LV filling pressure in different cardiac diseases.[4,5]

The current prospective study was designed first to assess the utility of several conventional Doppler and TDI parameters in the estimation of LV end diastolic pressure (LVEDP), and second trying to derive new index that may be useful for the non-invasive estimation of LV filling pressure.

2. Methods

Simultaneous LV pressure measurements and Doppler examinations were performed in 40 patients scheduled for elective coronary angiography to evaluate known or suspected coronary artery disease. Atrial fibrillation, mitral valve disease beyond mild severity, significant mitral annular calcification, and pericardial diseases were considered exclusion criteria in this study. All patients gave written informed consent before participation. The research protocol was approved by the local university review committee.

2.1. Echocardiography

This was performed with Philips iE33® (Philips Medical Systems, Andover, Massachusetts) echocardiographic machine within an hour before invasive assessment of LV filling pressures. A broad band 2.5–3.5 MHz phased array transducer equipped with TDI mode was utilized. Patients were studied in the supine position to match the position during invasive studies and ECG leads were connected to define timing of cardiac cycle events. Velocities were recorded for three consecutive cardiac cycles avoiding post ectopic beats, and results were averaged. All velocities were measured, whenever possible, during end expiration. Analysis of echocardiographic data was performed without the knowledge of hemodynamic findings.

2.1.1. Pulsed Doppler echocardiography

Mitral Flow patterns were recorded from apical four chamber views with 3–5 mm pulsed-sample placed between the tips of the mitral leaflets during diastole. Mitral inflow was analyzed for the following: peak E (early diastolic) and peak A (late diastolic) velocities, E/A ratio, and deceleration time of E wave (E-DT). Grades of LV diastolic dysfunction were defined according to current recommendation.[6]

2.1.2. TDI

In the apical 4 chamber view, a 4–5 mm sample volume was placed at the lateral margin of the mitral annulus and the cursor was oriented so that it is parallel to the direction of mitral annular motion. To ensure optimal accuracy, the wall filter was set at 100 Hz and the Nyquist limit was adjusted to a velocity range of 15–20 cm/s. Gains were minimized to allow for a clear tissue signal with minimal background noise. Annular motions were recorded at a frame rate of 80–140 frames per second and the sweep speed was set at 100 mm/s. Velocities and durations of early (E') and late (A') diastolic waves and peak systolic (S) wave were recorded and E'/A' ratio was calculated. Acceleration time of E' wave ($E'_{\text{Acc time}}$) was measured from onset to peak of E' wave and acceleration rate of E' wave ($E'_{\text{Acc rate}}$) was calculated as peak E' velocity divided by $E'_{\text{Acc time}}$. Similarly, deceleration time of E' wave ($E'_{\text{Decel time}}$) was measured from peak to end of E' wave and deceleration rate of E' wave ($E'_{\text{Decel rate}}$) was calculated as peak E' divided by $E'_{\text{Decel time}}$. Myocardial isovolumic relaxation time (IVRTm) was measured from the end of S wave to the onset of E' wave while myocardial isovolumic contraction time (IVCTm) was measured from the end of A' wave to the onset of S wave. In addition, the following derived ratios were computed: E/E', $E/E'_{\text{Acc time}}$, E/IVRT, and $E'/A'/S$. We tested the unifying equation proposed by Nageuh et al.[7] (PCWP $= 2 \pm 1.3$ mitral E/E') to predict measured LV filling pressure among our study cohort. Left ventricular ejection fraction was estimated by modified Simpson's rule.

2.2. Invasive measurement of LVEDP

LVEDP was directly measured by fluid-filled 6 F pigtail catheter introduced retrogradely via femoral artery into the cavity of LV. At the beginning of the study the pressure transducer was carefully calibrated at the 'zero' reference level. Pressure tracings were recorded before any contrast injection and were measured at the end of expiration. Pressure values were averaged as mean value of three consecutive sinus cycles and the beat-to-beat differences did not exceed 4 mm Hg. LVEDP was identified at the LV pressure tracing at the end of a wave.

LVEDP more than 15 mm Hg was defined as elevated pressure.

2.3. Statistics

SPSS software (version 13.0, SPSS Inc., Chicago) was used for statistical analysis. Continuous variables were expressed as median values (range) and categorical variables were presented as number (percent). Linear regression analysis was applied to examine the relation between LVEDP and Doppler parameters. A p value < 0.05 was considered significant. Intraobserver and interobserver variabilities were assessed in five randomly selected patients. Variability was expressed as the mean percent error, derived as the absolute difference between the two sets of observations, divided by the mean of the observations then intraclass correlation coefficient was obtained.

3. Results

3.1. Baseline characteristics

Baseline characteristics and hemodynamic data are summarized in Table 1. During data collection, the hemodynamics were stable, and no patient received continuous infusions of inotropic or vasopressor drugs with only two patients had sinus tachycardia (>100 bpm) at the time of study. Adequate LV pressure tracings were obtained in all patients. Five patients (12.5%) had LV ejection fraction lower than 40% and 29 patients (72.5%) had LV regional wall motion abnormalities. Specifically, basal segment of lateral left ventricular wall showed normal regional systolic function in all patients. All patients had LV diastolic dysfunction; median LVEDP was significantly higher in patients with grades II and III vs. patients with grade I dysfunction (30 vs. 13.2 mm Hg, $p < 0.001$).

Table 1 Baseline characteristics.

Variable	Median or no (%)	Range
Age (year)	55.5	42–70
Male	33 (82.5)	
Diabetes mellitus	21 (52.5)	
Systemic hypertension	14 (35)	
Systolic BP (mm Hg)	120	100–160
Diastolic BP (mm Hg)	70	60–100
Mean BP (mm Hg)	88.3	76.7–120
Heart rate (beats/min)	76	64–104
LVEDP (mm Hg)	28.5	5–45
Patients with LVEDP > 15 mm Hg	21 (52)	
Clinical diagnosis		
Acute coronary syndromes	27 (67.5)	
Heart failure	13 (32.5)	
LV ejection fraction (%)	48	30–85
LV diastolic dysfunction		
Grade I	20 (50)	
Grade II	12 (30)	
Grade III	8 (20)	

3.2. Correlation analysis

Adequate mitral inflow and tissue Doppler signals could be obtained in all patients. Linear correlations between LVEDP and different Doppler variables are shown in Table 2. Among all Doppler variables, E'/A' ratio showed the most significant and strongest correlation with LVEDP ($r = 0.612$, $p < 0.001$). Among patients with grades II and III diastolic dysfunction, E'/A' ratio showed significant good correlation with LVEDP ($r = 0.81$, $p < 0.001$) with the following regression equation: LVEDP = 1.77 + ($20.4 \times E'/A'$) (Fig. 1) while in patients with grade I diastolic dysfunction no correlation exists ($r = 0.11$, $p = 0.63$). Among those 29 patients with LV regional wall motion abnormalities, E'/A' ratio maintained its significant good correlations with LVEDP ($r = 0.65$, $p < 0.01$).

Other indexes that showed significant good correlations are A' velocity and all four conventional Doppler indices. Of note no correlation was detected between E' velocity and LVEDP; however when E wave velocity was indexed to E' to compute E/E' ratio a significant but weak correlation was detected ($r = 0.382$, $p = 0.016$) (Fig. 2).

As illustrated in Fig. 3, the three grades of diastolic dysfunction showed significant difference among the mean of E'/A' ratio (grade I: 0.73, grade II: 1.17, grade III: 1.4; p by ANOVA = 0.003). Furthermore significant difference was detected for E/E' ratio but not for E' velocity (grade I: 5.3, grade II: 6.4, grade III: 12.6; p by ANOVA = 0.003). Patients with elevated LVEDP (>15 mm Hg) had significantly higher median E'/A' ratio compared to patients with lower LVEDP (1.3 vs. 0.85, $p = 0.013$).

3.3. Validation of E/E' index

Applying the unifying equation proposed by Nageuh et al.[7] to estimate filling pressure in our patients, a weak albeit significant positive correlation was detected between the measured and calculated LVEDP ($r = 0.38$, $p = 0.01$). Among our patients, this unifying equation had 25% sensitivity and 94% specificity to identify patients with elevated LVEDP.

As regards the E/E' index, 5 (13%) patients had a ratio > 12 while 13 (32%) patients had a ratio < 8. The remaining 22 (50%) patients had an intermediate E/E' ratio (between 12 and 8). Patients with $E/E' > 12$ had significantly elevated median value of LVEDP (30 mm Hg) compared to those with $E/E' < 8$ (14.3 mm Hg, $p = 0.013$). An E/E' ratio > 12 had 25% sensitivity and 100% specificity to identify patients with elevated LVEDP with a positive predictive value of 100%. On the other hand, an E/E' ratio of <8 had 77% sensitivity and 57% specificity to identify patients with normal LVEDP with a negative predictive value of 31%.

3.4. Reproducibility

Intraobserver and interobserver variabilities for E'/A' ratio were 1.2% and 1.5% with intraclass coefficient of 0.97 and 0.95 ($p < 0.001$) respectively. Intraobserver and interobserver variabilities for E/E' ratio were 1.3% and 1.9% with intraclass coefficient of 0.93 and 0.91 ($p < 0.001$) respectively.

4. Discussion

The principal finding of the current study was that E'/A' ratio is the best index to estimate LVEDP especially in patients with advanced LV diastolic dysfunction, a relation that was not

Table 2 Linear regression correlation between LVEDP and Doppler indices.

Variable	Median (range)	r	p
Conventional pulsed Doppler			
E (cm/s)	67 (31–113)	0.585	< 0.001
A (cm/s)	57 (19–85)	−0.537	< 0.001
E/A	0.98 (0.6–5.6)	0.585	< 0.001
E-DT (ms)	150.65 (52–407)	−0.592	< 0.001
TDI			
E' (cm/s)	10.6 (6.7–25)	0.029	0.861
$E'_{\text{Acc rate}}$ (cm/s^2)	124 (50–292)	0.300	0.064
$E'_{\text{Acc Time}}$ (ms)	87.5 (45–230)	0.376	0.017
E′<ce:inf>Decel rate</ce:inf> (cm/s^2)	140 (46–1070)	−0.276	0.089
$E'_{\text{Decel time}}$ (ms)	80 (6.9–187)	−0.148	0.363
E' duration (ms)	161.8 (86–260)	−0.398	0.011
A' (cm/s)	11.3 (3.3–20)	−0.589	< 0.001
A' duration (ms)	111.5 (81–160)	0.287	0.072
IVRT m (ms)	80 (51–104)	0.221	0.170
IVCT m (ms)	72.5 (42–113)	−0.013	0.939
S (cm/s)	9 (5–16)	0.676	0.781
S duration (ms)	257 (180–320)	−0.045	0.676
E'/A'	1 (0.56–2)	0.612	< 0.001
E/E'	5.8 (0.5–15.5)	0.382	0.016
$E/E'_{\text{Acc time}}$	0.711 (0.02–1.3)	0.433	0.006
$E/E'_{\text{Acc rate}}$	0.757 (0.20–1.31)	−0.106	0.527
E/IVRTm	1 (0.4–1.6)	0.329	0.04
$E'/A'/S$	0.18 (0.04–0.41)	0.397	0.011

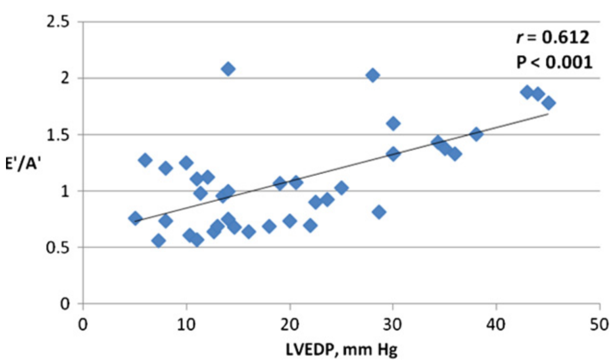

Figure 1 Scatter plot showing the correlation between LVEDP and E'/A' ratio.

found for other conventional or tissue Doppler variables including the E/E' ratio. A regression equation [LVEDP = 1.77 + (20.4 × E'/A')] was derived to predict LV filling pressure in patients with grades II and III LV diastolic dysfunction. Compared with other echocardiographic variables, E'/A' ratio has the following advantageous features for a reliable estimation of LV filling pressure: first, combining early to late mitral annular velocities provides more comprehensive evaluation of LV filling pressure throughout the diastole. Second, both E' and A' are minimally affected by preload.[8] Furthermore, both E' and A' waves reflect – and possibly correct for – a host of different factors that affect diastolic pressure (LV relaxation, systolic function, and LV minimal pressure for E' wave and LA contraction and relaxation, and LVEDP for A' wave).[6,8] Third, E'/A' ratio can be estimated from the same cardiac beat; this is in contrast to other combined Doppler indices (e.g. E/E') that must be estimated through two different cardiac beats.

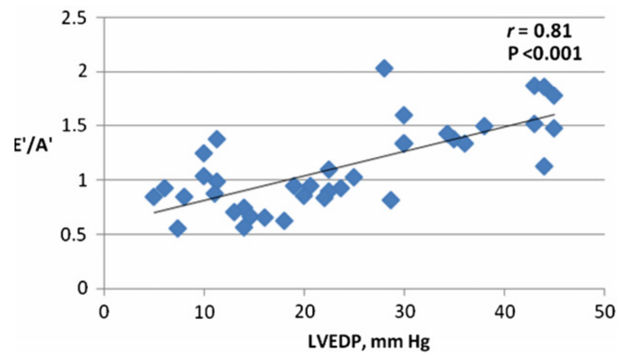

Figure 2 Correlation between E'/A' ratio and LVEDP in patients with advanced ventricular diastolic dysfunction.

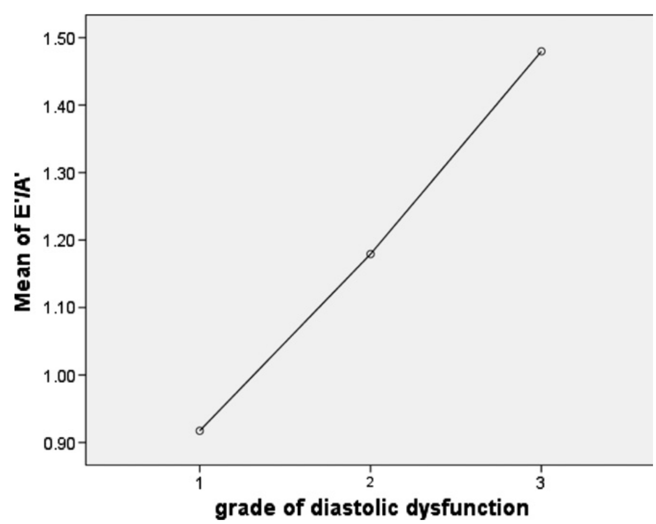

Figure 3 Relation between E'/A' velocity and different grades of LV diastolic dysfunction by ANOVA.

4.1. E/A′ ratio and LVEDP

In healthy young individuals the E'/A' ratio is > 1.6. In grade I diastolic dysfunction (impaired relaxation; IR), there is decrease in E' velocity and increase in A' velocity with a decrease in E'/A'.[9] With progressive diastolic dysfunction, A' velocity decreases and $E'/A' \geqslant 1$.[10]

The improved performance of E'/A' ratio among our patients with advanced LV diastolic dysfunction, rather than patients with IR pattern, can be explained by the fact that patients with IR pattern, who constituted 50% of our patients, usually have normal or mildly elevated LV filling pressure at rest 11 and accordingly inclusion of these patients in the analysis is suspected to weaken the correlation between E'/A' ratio and LVEDP. In accord with this, no correlation was detected between E'/A' ratio and LVEDP among our patients with IR pattern.

Use of E'/A' ratio to predict LVEDP is accordingly based upon initially identifying patients with normal or IR transmitral flow pattern by pulsed Doppler. This copes with recent guidelines recommending the use of both conventional pulsed and tissue Doppler for the assessment of LV diastolic dysfunction and estimation of LV filling pressure.[6]

4.1.1. Prior studies
Little and contradictory data exist regarding the relation between E'/A' ratio and LV filling pressures. In a study by Lindqvist et al., among 32 patients E'/A'_{Septal} showed significant *positive* correlation with PCWP ($r = 0.52$, $p < 0.05$).[12] In a study by Kasner et al., among 42 patients with diastolic heart failure, $E'/A'_{Lateral}$ showed *negative* correlation with LVEDP ($r = -0.42$, $p < 0.004$).[13] In a study by Nageuh et al., among 100 patients there was *no* significant correlation between $E'/A'_{Lateral}$ and PCWP.[7] This discrepancy between studies may be explained by the inclusion of participants with a narrow range of LV diastolic dysfunction. Significant proportion of patients in the preceding studies had IR (with $E'/A' < 1$) or pseudonormal (E'/A' still reversed or approaching 1) filling patterns while restrictive pattern ($E'/A' > 1$) is seldom presented in these studies. For instance, in the study of Kasner et al. among the study cohort, 38 patients (88%) had IR pattern and the remaining 5 patients had pseudonormal pattern.[13] Similarly in the study of Nageuh et al., all patients had either IR or pseudonormal flow patterns.[7] In contrast, 30% and 20% of patients in our study had pseudonormal or restrictive flow patterns respectively. This may explain the significantly higher median LVEDP in our study compared with the above studies. This also copes with the finding that one third of our patients had advanced heart failure (NYHA III–IV).

4.2. E/E' ratio and LV filling pressure

In our study the correlation between E/E' ratio and LVEDP was less robust ($r = 0.38$, $p = 0.016$) than previously reported. Similarly, when we tested the unifying equation proposed by Nageuh et al.[7] in our study cohort, a weak albeit significant positive linear correlation was detected between the measured and calculated LVEDP.

4.2.1. Prior studies
Numerous clinical studies have shown a positive, linear relation of E/E' with invasively determined LV filling pressure regardless of LV ejection fraction, rhythm and heart rate.[7,14] However, in concordant with our results, many studies reported weak correlations between E/E' ratio and LV filling pressure. Ommen et al. reported modest correlation between $E/E'_{Lateral}$ ($r = 0.51$) and mean LVDP.[5] In another study by Bruch et al., weak correlation was detected between $E/E_{Average}$ and PCWP in patients with systolic heart failure ($r = 0.47$, $p < 0.001$).[15] Lindqvist et al. found a weak correlation between E/E' and PCWP at lateral, septal and anterior walls ($r = 0.43$–0.44, $p < 0.05$).[12] Similarly, Hadano et al. reported poor correlation between $E/E'_{Lateral}$ and LVEDP ($r = 0.33$, $p < 0.001$) among 140 patients referred for cardiac catheterization.[16] Mullens et al. reported a poor correlation between E/E' ratio and PCWP ($r \leqslant 0.27$) in 106 patients with advanced decompensated heart failure (LVEF $\leqslant$ 30%) and in patients with E/E' ratios < 8, 8 to 15, and > 15, average PCWPs were similar (19 ± 4, 19 ± 7, and 20 ± 6 mm Hg, respectively). When the investigators tested the unifying equation proposed by Nageuh et al. to predict measured PCWP in the study cohort, no correlation was observed ($r = 0.03$, P = NS).[17] E/E' ratio was reported to be unreliable for predicting LV filling pressure in normal hearts[18] or in patients with hypertrophic cardiomyopathy,[19] primary mitral regurgitation,[20] or constrictive pericarditis.[21]

Different cut-offs for E/E' ratio ranging between 9 and 16 have been reported for predicting elevated LV filling pressure in patients with different LV statuses.[22–24] Furthermore, E/E' ratio is unreliable for predicting LV diastolic pressures in patients with ratios between 8 and 15. This is important since about 51% of patients were reported to have this intermediate E/E'.[5] Interestingly, similar proportion of our patients had E/E' ratio in the gray zone[8–12] that may explain the poor sensitivity (25%) of $E/E' > 12$ to detect patients with elevated LVEDP.

4.3. Limitations

The study was performed in a consecutive but not diagnosis specific group of patients; however this makes the findings of our study applicable to different patients frequently encountered in daily practice. All patients were referred for clinically indicated reasons and therefore only a small percentage of them had normal LV pressure. Despite this limitation, the range of baseline hemodynamics was wide. The obtained regression equation to estimate LVEDP should be validated in a large cohort of patients. Velocities were recorded along the lateral mitral annulus. Recording of lateral annular velocities is easier, more reproducible, less preload dependent and may be less influenced by the right ventricle through common interventricular septum.[12,18]

5. Conclusion

Of all echocardiographic variables investigated, E'/A' ratio was identified as is the best index to estimate LVEDP especially in patients with advanced LV diastolic dysfunction; a relation that was not found for other conventional or tissue Doppler variables including the E/E' ratio.

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